Tetrahedron, 1959, Vol. 7 pp. 277 to 288 Pergamon Press Ltd. Printed in Northern Ireland

POLYMORPHISM IN SUBSTITUTED BARBITURIC ACIDS

B. CLEVERLEY and P. P. WILLIAMS
Dominion Laboratory, Department of Scientific and Industrial Research,
Wellington, New Zealand

(*Received* 14 *April* 1959)

Abstract—Of twenty substituted barbituric and thiobarbituric acids studied, nine have been found to exist in polymorphic forms. These are barbital, butethal, amobarbital, pentobarbital, thiopental, phenobarbital, aprobarbital, nostal and kemithal. The different modifications have been studied by X-ray diffraction and infra-red spectrophotometry, and the transition temperature ranges have been determined. The forms found are divided into two groups on the basis of their infra-red spectra. The tautomeric form of the compounds in the solid state is discussed briefly.

INTRODUCTION

POLYMORPHISM in substituted barbituric acids has been previously reported by a number of workers[1-5] in greater or less detail. This paper embodies the results of investigations of twenty such compounds, all commonly used in pharmaceutical preparations. All the acids are 5,5 disubstituted with a variety of alkyl and aryl substituents, two are N-methyl derivatives, and three are 2-thiobarbituric acids.

The trivial names used here are those adopted by *Chemical Abstracts*, and have been tabulated with synonyms and chemical names by Williams.[6]

EXPERIMENTAL

The techniques used for preparation of polymorphic forms were fusion, and crystallization of the supercooled melt, (if one formed) at different temperatures, precipitation from aqueous alkaline solution by acidification, crystallization from diethyl ether, and from aqueous alcohol, and evaporation of solutions in carbon tetrachloride, and chloroform, by blowing a jet of air over the solution to give rapid crystallization at low temperatures. All products were characterized by their X-ray diffraction patterns. Thermally unstable or metastable modifications were heated for an hour at 40°, 50°, etc. up to fusion, and examined after each step.

X-ray patterns were obtained on a Norelco wide range Geiger Diffractometer, using nickel filtered copper radiation (1·5418 Å). Infra-red spectra were obtained on a Perkin–Elmer Model 21 double-beam spectrophotometer. The samples were prepared as paraffin mulls and hexachlorobutadiene mulls, confined between two rocksalt plates. Sodium chloride optics were used. The infra-red spectra of different modifications in chloroform solution all at the same concentration, were also obtained.

The reversibility of the thermal transformation of one form to another was investigated by slowly cooling the more stable form through the transformation temperature range, and in some cases by cooling it to liquid air temperatures. The product was then examined for traces of the less stable form.

RESULTS

Of the twenty barbituric acids studied, nine were found to be polymorphic. These compounds are listed in Table 1, together with the methods of preparation of the different forms. The other

[1] R. Fischer, *Ber. Dtsch. Pharm. Ges.* **270**, 149 (1932).
[2] R. Fischer and A. Kofler, *Ber. Dtsch. Pharm. Ges.* **270**, 207, (1932).
[3] Maria Brandstatter, *Z. Phys. Chem.* **A191**, 227 (1942).
[4] T-Y. Huang, *Acta Pharm. Intern.* **2**, 43, (1951).
[5] T-Y. Huang, *Acta Pharm. Intern.* **2**, 95 (1951).
[6] P. P. Williams, *Analyt. Chem.* **31**, 140 (1959).

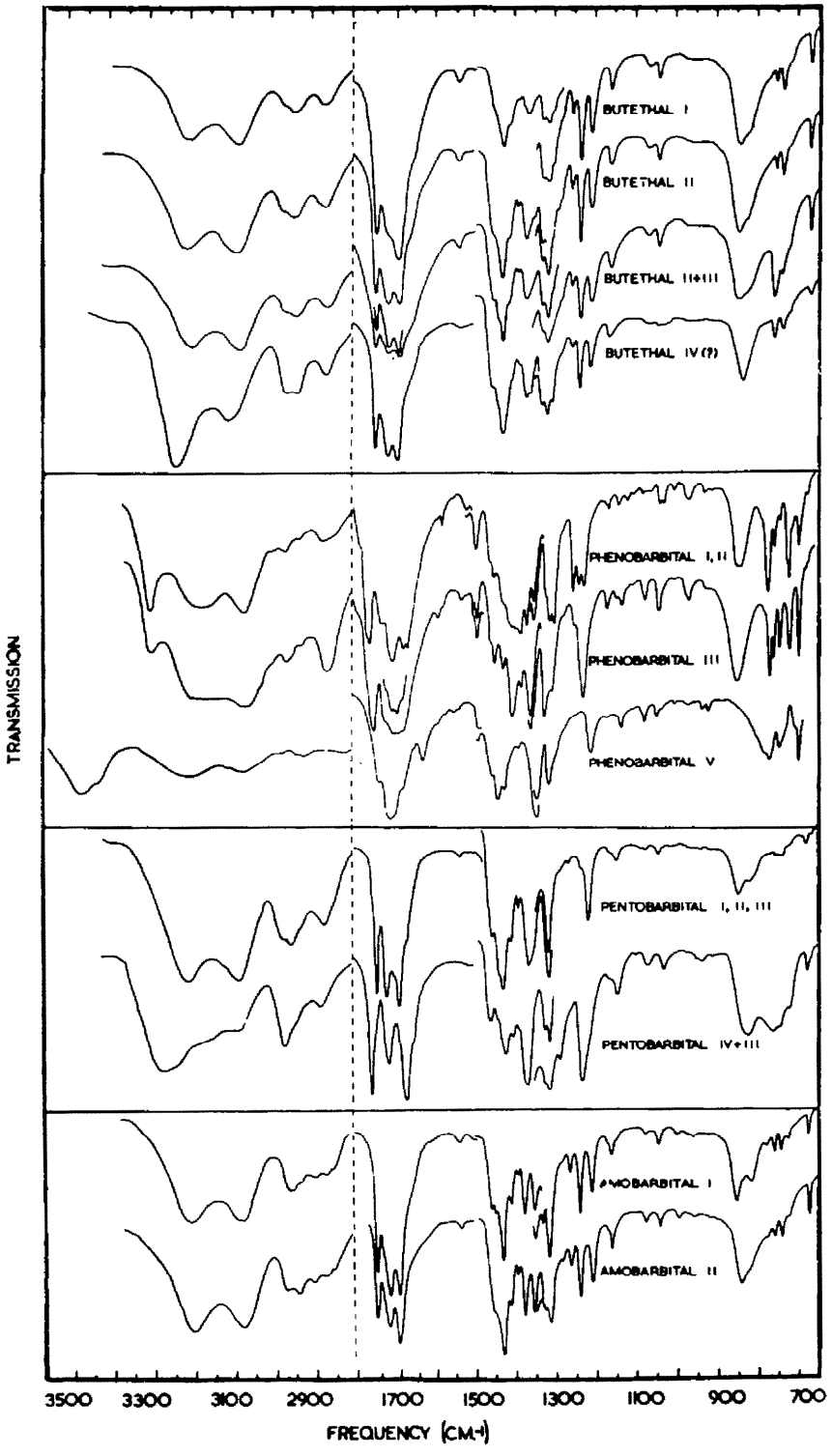

FIG. 1. Infra-red spectra of polymorphic barbituric acids, recorded between 4000–650 cm^{-1}. Hexachlorobutadiene used as a mulling liquid in regions of paraffin oil absorption. A break in the curve indicates a change in sample concentration or of mulling liquid.

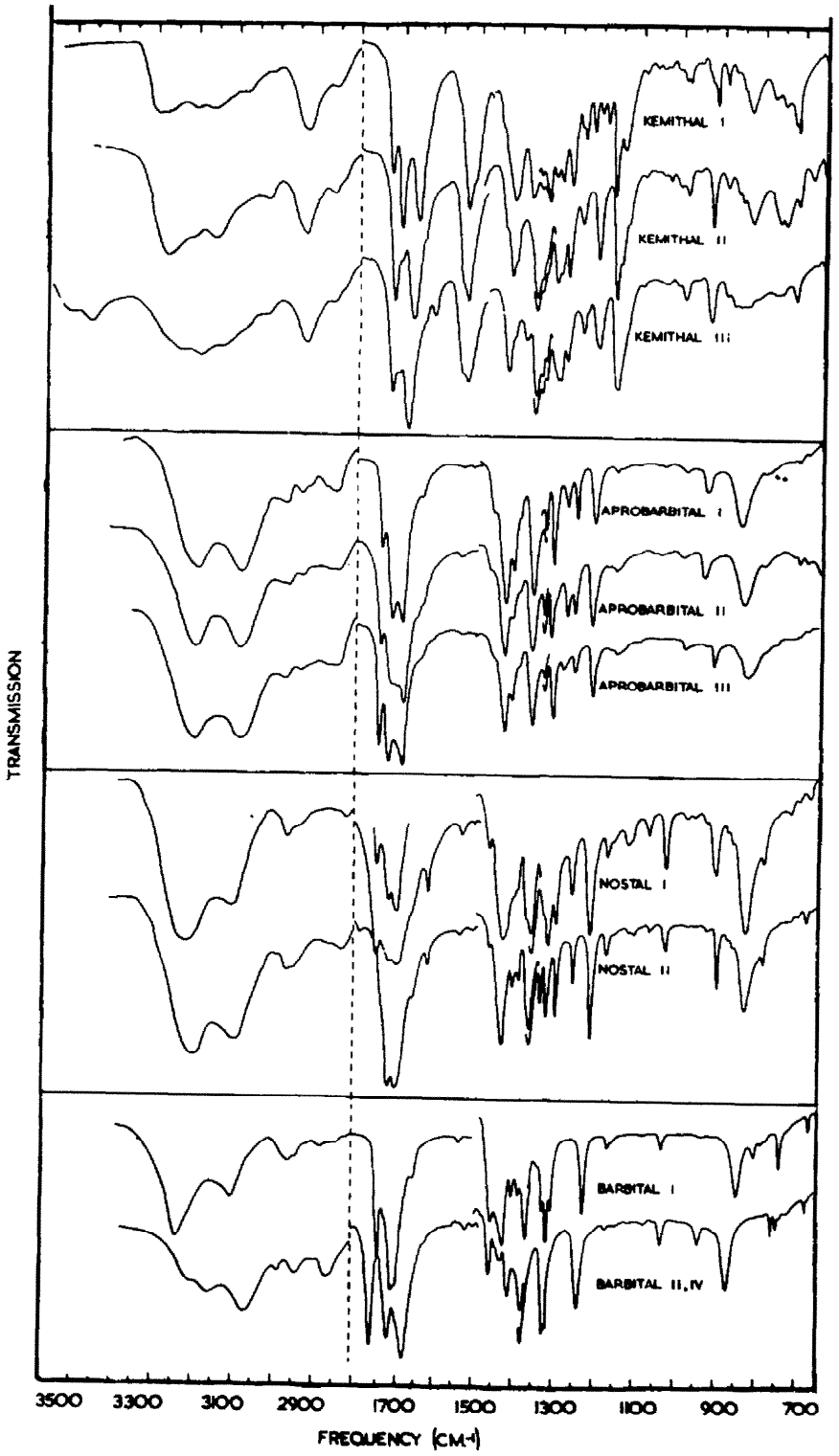
KEMITHAL I
KEMITHAL II
KEMITHAL III
APROBARBITAL I
APROBARBITAL II
APROBARBITAL III
NOSTAL I
NOSTAL II
BARBITAL I
BARBITAL II, IV
TRANSMISSION
3500 3300 3100 2900 1700 1500 1300 1100 900 700
FREQUENCY (CM-1)

FIG. 1. (*cont.*)

TABLE 1

Compound	Room temp	40°	50°	60°	70°	80°	90°	100°	110°	120°	130°	140°	150°	160°	170°	180°
Barbital	IV[a]	IV	IV	IV	IV (+II)	IV + II	IV + II	II	II	II	II	II + I	I	I	I	I
Butethal	III + II[b] II[c]	III + II II	III + II II	III + II + I II + I	I I	I I	I I	I I	I I	I I						
Amobarbital	II[d]	II	II	II	II	II	II	II	II	II	II + I	I	I			
Pentobarbital	IV + I[f] III[c] II[g]	IV + I III II	IV + I III II	IV + I III II	IV + I III + II + I II	(IV+) I II + I II + I	I II + I II + I	I II + I II + I	I II + I II + I	I I I						
Thiopental	II[g]	II	II	II	II	I	I	I	I	I	I	I				
Phenobarbital	V[a]	V + III	V + III	III	III	III	III	III	III	III	II + I	II + I	II + I	I	I	
Aprobarbital	III[b]	III	III + II	III + II	II	II	II	II + I	II + I	II + I	I					
Nostal	II[d] I[h]	II I	II I	II I	II I	II I	II I	II I	II I	II I	II I	II I	II I	II I	II I	
Kemithal	III[a]	III	III	III	III + II	II	II	II	II + I	I	I					

[a] Precipitated from alk. soln. by acidn.
[b] cryst. from chloroform
[c] crystn. of supercooled melt at room temp.
[d] cryst. from diethyl ether
[h] fused
[f] cryst. from chloroform under air jet
[g] cryst. from carbon tetrachloride under air jet

eleven, butabarbital, cyclobarbital, cyclopal, dial, hexobarbital, mephobarbital, probarbital, rutonal, sandoptal, secobarbital and thiamylal did not give polymorphic forms with the methods used. X-ray patterns not previously published are presented in Table 2, and the distinct infra-red patterns in Fig. 1. Table 1 shows the results of heating a less stable modification for an hour at a time to regularly increasing temperatures, and cooling to room temperature for X-ray examination between steps. Where two modifications co-exist over a range of temperatures, the proportion of the more stable one increases with rising temperature.

All the thermal transformations were irreversible under the experimental conditions used. However, since all examinations were carried out at room temperature, the actual behaviour at higher temperatures is not necessarily known.

The infra-red spectra of different forms of a compound in chloroform solution were always identical, showing that the various crystallization techniques did not result in decomposition.

Details of the modifications studied are as follows:

Barbital (*5,5-diethyl barbituric acid*). Huang[6] has published X-ray patterns for four forms, only three of which (I, II and IV) were prepared in this work. Forms II and IV have similar X-ray patterns, and identical infra-red spectra. Form I is quite different from these, both in its X-ray pattern, and over the whole range of the infra-red spectrum. Grinding form II results in its transformation to form I.

Butethal (*5-ethyl-5-n-butyl barbituric acid*). Four forms have been prepared. X-ray patterns of forms I[6] and II[7] have already been published, but redetermination of that of form II showed discrepancies from Huang and Jerslev's data, and the revised pattern appears in Table 2. Modification IV was formed in small quantities with form II by rapid evaporation of a carbon tetrachloride solution with a jet of air. It has not been studied in detail, but its X-ray pattern is characterized by lines at 9·05 (m), 7·83 (mw), 6·42 (mw), 5·63 (w), 4·35 (s), 3·85 (mw) and 2·98 Å (m). The X-ray patterns of forms I and II are similar, and the infra-red patterns show only slight differences in the C=O stretching and C—H bending regions. Form III was prepared only in association with form II, and some lines ascribed to form II are present in the X-ray pattern in Table 2. This pattern is quite different from those of I and II, and the infra-red spectrum of III differs from those of I and II in the region 900–700 cm^{-1}. Grinding a mixture of forms II and III resulted in a form giving an infra-red spectrum different from the others, particularly in the N—H stretching region. This may be due to form IV, but X-ray verification of this was impracticable. Form I is transformed to form II very easily by grinding.

Amobarbital (*5-ethyl-5-isoamyl barbituric acid*). Two forms have been found. The X-ray pattern of form I (which can be prepared by crystallisation from chloroform) has been published,[6] and differs markedly from that of form II. The differences in the infra-red patterns are small, being intensity differences in the C=O stretching and C—H stretching and bending regions, and some peak shifts in the region 900–700 cm^{-1}.

Pentobarbital (*5-ethyl-5-(1-methyl butyl) barbituric acid*). Brandstatter[5] has reported the existence of two forms. The X-ray pattern of form II is closely similar to that published by Huang and Jerslev,[7] but this pattern is given in Table 2, to emphasize its similarity to that of form III. The differences between these patterns are the splitting of certain peaks in form II to produce doublets in III. This suggests that one modification may be a disordered form of the other. The X-ray pattern of I is similar in many respects to both these. These similarities are reflected in the identity of the infra-red spectra of all these three forms. Pentobarbital IV was invariably contaminated to a certain extent by form I, but as the X-ray patterns of both are fairly simple, that of form IV can be reported with some certainty. It is possible that weak reflections from IV occur at the same positions of strong ones from I. The infra-red spectrum of IV differs from that of the other forms over the whole spectrum. The infra-red and X-ray patterns of pentobarbital II and III bear a strong resemblance to those of amobarbital I, suggesting that these are structurally similar. The thermal transition of form III to form I outlined in Table 1 probably involves form II, but the similarity between II and III makes this difficult to determine with certainty.

Thiopental (*5-ethyl-5-(1-methyl butyl)-2-thiobarbituric acid*). Two forms have been found. The X-ray pattern of form I has been published[6] and is somewhat similar to that of form II. The infra-red spectra of the two are identical.

[7] T-Y. Huang and B. Jerslev, *Acta Pharmacol et Toxicol.* 7, 227 (1951).

TABLE 2

Amobarbital I		Aprobarbital IV		Butethal II	
d	I/I_1	d	I/I_1	d	I/I_1
11·25	90	9·1	100	10·7	54
9·90	100	5·91	26	9·75	100
8·95	14	5·21	10	7·25	37
7·9	2	5·04	8	6·93	77
7·45	2	4·54	15	5·98	8
6·98	69	4·09	5	5·37	66
6·24	4	3·66	19	5·14	9
5·96	30	3·37	33	4·99	5
5·52	96	3·03	100	4·85	29
5·37	19	2·88	5	4·47	18
4·98	19			4·33	6
4·87	30			4·07	4
4·78	26			3·99	39
4·54	12			3·93	3
4·46	23			3·74	6
4·38	2			3·67	2
4·19	44			3·60	25
3·76	73			3·45	4
3·68	16			3·31	8
3·63	21			3·18	13
3·56	4			3·09	6
3·50	12			2·95	5
3·27	11			2·91	4
3·20	2			2·81	2
3·17	5			2·680	6
3·10	45			2·570	7
3·05	14			2·490	3
3·00	6				
2·94	3				
2·88	2				
2·827	20				
2·760	3				
2·735	6				
2·686	8				
2·555	8				
2·540	9				
2·508	2				
2·450	4				
2·424	5				
2·344	3				
2·298	2				
2·191	2				
2·005	2				
1·985	4				
1·883	3				

TABLE 2 (*cont.*)

Butethal III		Kemithal I		Kemithal II	
d	I/I_1	*d*	I/I_1	*d*	I/I_1
20·2	21	15·2	30	13·0	76
11·5	81	12·5	20	6·93	100
10·6	11 (II)	8·75	5	6·70	49
10·15	100	8·45	5	6·49	15
9·85	23 (II)	7·97	25	6·24	5
9·30	38	7·70	25	6·07	5
8·88	6	7·53	10	5·79	27
8·28	5	6·51	10	5·45	84
7·50	5	6·28	20	5·25	5
7·28	5 (II)	6·15	10	5·08	36
7·12	23	6·07	10	4·96	3
6·90	27 (II)	5·91	10	4·67	24
6·62	21	5·80	20	4·55	14
6·38	39	5·68	35	4·41	5
5·34	90	5·54	10	4·33	9
5·08	29	5·23	100	4·22	14
4·86	18	5·01	10	4·09	12
4·74	15	4·93	10	4·05	30
4·43	20	4·75	5	3·91	15
4·18	27	4·67	10	3·82	41
4·06	30	4·57	15	3·69	9
3·99	36	4·54	15	3·63	7
3·95	9	4·41	10	3·52	48
3·82	86	4·32	10	3·42	63
3·67	18	4·13	20	3·34	7
3·50	26	4·04	10	3·27	31
3·45	9	3·96	10	3·11	19
3·40	8	3·83	20	3·07	9
3·31	11	3·77	5	2·97	24
3·26	5	3·72	10	2·92	7
3·23	5	3·66	20	2·875	7
3·17	6	3·53	20	2·815	10
3·10	9	3·49	20	2·785	9
3·00	20	3·42	20	2·633	5
2·96	23	3·39	15	2·533	10
2·91	15	3·32	10	2·500	5
2·875	5	3·21	30	2·462	10
2·806	5	3·13	20	2·355	3
2·747	3	2·825	15	2·338	3
2·565	5	2·706	5	2·302	7
		2·501	10	2·020	5
				1·993	3

TABLE 2 (*cont.*)

Nostal I		Pentobarbital I		Pentobarbital II	
d	I/I_1	*d*	I/I_1	*d*	I/I_1
11·9	62	11·25	100	11·05	100
7·52	8	7·94	20	10·05	25
6·45	65	7·35	16	8·9	17
6·28	18	7·02	81	7·04	87
5·95	94	6·71	2	6·46	8
4·74	62	6·15	2	5·60	72
4·68	24	5·53	61	5·48	87
4·61	8	5·11	3	5·04	6
4·48	10	4·99	9	4·84	57
3·96	33	4·83	34	4·66	6
3·88	10	4·48	11	4·51	17
3·81	22	4·21	3	4·26	6
3·62	27	4·15	2	3·82	6
3·56	41	4·02	7	3·67	36
3·43	24	3·96	2	3·30	4
3·29	14	3·76	36	3·25	4
3·23	33	3·71	7	3·15	8
3·20	9	3·66	3	3·04	21
3·14	100	3·57	18	2·817	19
3·09	4	3·51	16	2·747	4
2·99	39	3·42	3	2·563	9
2·92	8	3·38	2	2·548	6
2·734	8	3·23	2		
2·694	19	3·18	7		
2·502	12	3·14	4		
2·301	12	3·03	16		
2·238	12	2·92	2		
2·174	5	2·865	4		
1·949	5	2·822	18		
1·908	4	2·732	7		
		2·550	11		
		2·483	3		
		2·408	2		
		2·325	2		
		2·294	2		
		2·109	3		
		1·992	3		

TABLE 2 (*cont.*)

Pentobarbital III		Pentobarbital IV		Phenobarbital V	
d	I/I_1	*d*	I/I_1	*d*	I/I_1
11·2	45	13·8	88	15·4	100
10·85	100	6·21	100	12·3	2
10·1	55	6·07	40	8·94	2
9·9	40	5·07	31	7·75	64
8·86	23	4·92	44	6·5	1
7·95	8	4·66	23	6·3	1
7·13	57	4·29	20	5·90	72
6·83	45	3·95	10	5·45	49
5·83	6	3·74	33	5·17	20
5·62	54	3·28	6	5·04	1
5·44	88	2·94	15	4·75	14
4·84	42	2·865	15	4·68	4
4·52	17	2·635	5	4·45	1
4·09	18	2·620	5	4·33	2
4·00	19			4·18	1
3·71	11			4·11	1
3·61	37			4·02	2
3·43	3			3·91	94
3·41	5			3·76	5
3·25	3			3·56	17
3·16	9			3·50	8
3·08	3			3·39	7
3·03	17			3·33	2
2·96	6			3·25	3
2·91	3			3·16	2
2·82	15			3·09	28
2·707	7			2·98	34
2·574	6			2·868	14
2·542	8			2·788	34
1·994	8			2·749	4
				2·690	10
				2·615	10
				2·588	7
				2·483	4
				2·423	1
				2·410	1
				2·367	3
				2·341	3
				2·331	3
				2·281	1
				2·225	7
				2·166	3
				2·147	2
				2·094	1
				2·080	1

TABLE 2 (*cont.*)

Pentobarbital III		Pentobarbital IV		Phenobarbital V	
d	I/I_1	*d*	I/I_1	*d*	I/I_1
				2·063	3
				2·015	3
				1·997	1
				1·983	2
				1·931	6
				1·865	2
				1·824	2
				1·719	2
				1·701	1
				1·675	1
				1·666	1
				1·643	1
				1·626	1
				1·606	1
				1·546	1

Thiopental II	
d	I/I_1
13·5	100
6·76	22
6·37	3
6·07	4
5·10	9
4·79	3
4·45	3
4·34	7
4·04	2
3·90	4
3·77	2
3·33	3
3·14	3

Phenobarbital (*5-ethyl-5-phenyl barbituric acid*). Six forms are now known. Huang[4] has reported X-ray patterns for forms I, II, III, IV and IVa, and the pattern of a new form, V, appears in Table 2. Forms IV and IVa were not prepared in this work. Forms I and II have similar X-ray patterns and identical infra-red spectra. Forms III and V are very different from these, and from each other, both in X-ray patterns and over the whole infra-red spectrum. Phenobarbital II is readily convertible to form III on grinding, and form V will slowly change to III, spontaneously.

Aprobarbital (*5-allyl-5-isopropyl barbituric acid*). Four forms have been reported; X-ray patterns of I, II and III have been reported by Huang,[5] and the preparation of IV by Williams.[8] Form IV is

[8] P. P. Williams, *Nature, Lond.* **179**, 1189 (1957).

most unstable, reverting to III when dry, and has not been studied in detail. The X-ray pattern of the wet crystals is given in Table 2. Forms I, II and III have quite different X-ray patterns and show differences in their infra-red spectra. The spectra of forms I and II differ in the relative intensities of peaks in the 1300–1200 cm^{-1} region, and that of III differs from these in the C=O stretching and C—H bending regions, and in the 900–850 cm^{-1} region.

Nostal (*5-isopropyl-5-(2-bromallyl) barbituric acid*). Two forms have been prepared. The pattern of II already reported[8] is quite different from that of I, and their infra-red spectra show differences in the C=O stretching and C—H bending regions. Both I and II are thermally stable, but form I readily changes to II on grinding.

Kemithal (*5-allyl-5-cyclohexenyl-2-thiobarbituric acid*). Three forms have been prepared. Forms I and II can be prepared only by heating III. The X-ray patterns of all three (that of form III has been previously published[6]) are quite distinct. The spectra of I and II differ only below 1800 cm^{-1}, whereas that of form III differs markedly from these in the N—H stretching region. Below 1800 cm^{-1}, II and III are similar, showing small differences in the C=O stretching and 900–650 cm^{-1} regions.

DISCUSSION

It has been observed in this work that major differences in the infra-red spectra of different modifications of the same compound are invariably accompanied by major differences in the X-ray pattern. Any similarity between the X-ray patterns is always reflected in a very close similarity or identity in the infra-red spectra.

No correlation is apparent between molecular structure, and the occurrence of polymorphism in these compounds. For example, phenobarbital occurs in six known modifications, and yet mephobarbital (N-methyl phenobarbital) is monomorphic. This suggests that the N-hydrogen atom is involved in intermolecular bonding in at least some of the forms of phenobarbital. However, the monomorphism of rutonal (5-methyl-5-phenyl barbituric acid) is more difficult to explain. The monomorphism of dial (5,5-diallyl barbituric acid) is rather surprising in view of the tetramorphism of barbital. Although Hertel[9] reports that dial and barbital II have very similar structures, attempts to form other barbital-like structures with dial, by seeding dial melts with different forms of barbital, and by forming mixed crystals, met with no success. On the other hand, despite the tetramorphism of aprobarbital, it would have been expected that the introduction of a bromine atom on the allyl group to form nostal would have stabilized the structure, and produced a monomorphic compound. The fact that the two forms of nostal are not interconvertible by heat alone is almost certainly due to the presence of the large bromine atom. The trimorphism of kemithal is also rather surprising in view of the large molecule and the availability of only two carbonyl groups for intermolecular bonding.

Comparison of the infra-red spectra of different forms of the same compound shows that large differences in the C=O stretching region are almost always accompanied by large differences in the C—H bending region. This suggests that such a change in the C=O region, caused by a major rearrangement of the molecules in the lattice, is accompanied possibly by changes in molecular symmetry, and by a redisposition of the C_5 substituents, thereby modifying the selection rules governing the appearance and intensity of peaks.

A large group of spectra are almost identical in the N—H stretching region—two almost equally intense peaks at about 3200 and 3080 cm^{-1}. The same two peaks characterize the solution spectra in chloroform at high concentration,[10] when the monomer N—H stretching peak at 3360 cm^{-1} is reduced in intensity, and they are also typical of the spectra of cyclic amides.[11] The carbonyl bands of this group of modifications usually consist of three simple peaks, and are again, rather like the carbonyl bands of the solution spectra.[10] The spectra concerned are those of nostal I and II, amobarbital I and II, aprobarbital I, II and III, pentobarbital I, II and III, and butethal I, II and III.

A strong, sharp band at around 840 cm^{-1} is associated with the spectra of solid barbiturates,[12] and a broad band in this region is observed in solution spectra.[10] This is undoubtedly the band of similar appearance, due mainly to the N—H out-of-plane bending vibration, observed at 700–750 cm^{-1} in monosubstituted amides and at 840 cm^{-1} in cyclic amides.[13] This band is similar in all the first group of modifications.

[9] E. Hertel, *Z. Phys. Chem.* Abt. B. 117 (1935).
[10] C. J. Umberger and Grace Adams, *Analyt. Chem.* **24**, 1309 (1952).
[11] S. E. Darmon and G. B. B. M. Sutherland, *Nature, Lond.* **164**, 440 (1949).
[12] L. Levi and C. E. Hubley, *Analyt. Chem.* **28**, 1591 (1956).
[13] T. Miyazawa, T. Shimanouchi and S. Mizushima, *J. Chem. Phys.* **24**, 408 (1956).

The remaining spectra (excluding those of thiobarbituric acids) are often greatly different from one another and from the first group in the N—H and C=O regions. Large differences in N—H spectra between modifications of the same compound are generally paralleled by large differences in the C=O region. This suggests that the N—H:C=O intermolecular interaction is important in these structures. Some of these spectra are very complex in the N—H and C=O regions, suggesting a complex system of intermolecular interactions, and it may be significant that there appears to be some degree of correlation between such complexity, and the occurrence of large spacings in the X-ray pattern.

Enolization could be a factor contributing to the polymorphism found, but the occurrence of N—H stretching and out-of-plane bending vibrations in the first group of spectra, at the characteristic frequencies of keto amides, and the absence of any absorption at a frequency high enough to be assigned to an O—H stretching vibration, indicates that these compounds exist in the solid and in chloroform solution as the keto forms.

Although the hydrogen stretching regions of the second group of spectra differ from those of the first group, it is only in phenobarbital V and kemithal III that peaks occur that are likely to arise from O—H stretching vibrations. It may be significant that it is only in the spectra of these two modifications that the N—H out-of-plane bending vibration appears to be anomalous. Unlike the other modifications of these compounds these two show a peak at around 1620 cm^{-1}. A similar peak in the spectrum of acetyl urethane led to the suggestion that this latter compound is completely enolized.[14] Although phenobarbital and kemithal contain unsaturated C_5 substituents, no absorption appears in this region of their other modifications.

It therefore seems probable that in phenobarbital V and kemithal III enolization has occurred, but the infra-red evidence favours the triketo configuration for all the other modifications.

[14] H. M. Randall, R. G. Fowler, N. Fuson and J. D. Dangl, *Infra-Red Determination of Organic Structures*, Van Nostrand, New York (1949).